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10/089,027	03/26/2002	William E. Jack	NEB-166-PUS	9409

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HARRIET M. STRIMPEL, D. Phil.
New England Biolabs, Inc.
240 COUNTY ROAD
IPSWICH, MA 01938-2723

EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
12/29/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

STRIMPEL@NEB.COM
Goldberg@neb.com
nardone@neb.com

Office Action Summary	Application No.	Applicant(s)	
	10/089,027	JACK ET AL.	
	Examiner	Art Unit	
	Richard G. Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *32-43* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment of claim 32, in the paper of 10/29/2010, is acknowledged. Claims 32-43 remain pending and at issue for examination.

Applicants' arguments filed on 10/29/2010, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Applicant's election of the species of SEQ ID NO: 5, in the paper of 2/11/2008, continues to be acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-42 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising providing a DNA Polymerase selected from the group consisting of Vent, Deep Vent, *Pfu* and 9°NTM or the specifically disclosed variants referred to in claim 43, with a template, a primer that binds to the template and a nucleotide solution containing at least one acyclonucleotide and incubating the DNA polymerase with the template and the nucleotides so that the DNA polymerase extends the primer by incorporating the nucleotides, does not

reasonably provide enablement for any method comprising providing a DNA Polymerase having an amino acid sequence that shows a mere 30% overall identity with that of SEQ ID NO: 4 and further includes a 15 amino-acid motif that is identical to SEQ ID NO: 5-22 except that it contains up to 3 amino acid substitutions as compared with the SEQ ID NO, with a template, a primer that binds to the template and a nucleotide solution containing at least one acyclonucleotide and incubating the DNA polymerase with the template and the nucleotides so that the DNA polymerase extends the primer by incorporating the nucleotides The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The rejection is stated in the previous office action as it applied to previous claims 32-42. In response to this rejection applicants have amended claim 32 and continue to traverse the rejection as it applies to the newly amended claims.

Applicants continue to traverse this rejection on much the same basis as previously submitted. Applicants submit that enablement of the claimed invention relies on reviewing the specification supporting the claims. Applicants submit that the specification provides a comprehensive description of the class of polymerases defined in the claims, an assay (Example 1) now incorporated into the amended claim 32 and their use with a specific modified nucleotide, namely, an acyclonucleotide.

Applicants submit that the Dr. Jack declaration states that the claimed method of using acyclonucleotides is applicable for a highly conserved group of polymerases

that has been structurally and functionally defined in the claims and in the specification.

Applicants further submit that the Dr. Jack declaration provided under oath and dated May 4, 2006 states the following in paragraph 8:

> "I assert that the combination of the high degree of homogeneity in DNA and amino acid sequences of archeaon DNA polymerases plus the structural evidence that modification of specific amino acids alters enzyme specificity would be sufficient to assure a person of ordinary skill in the art that the class of polymerases as defined above will interact with acyclonucleotide substrates as shown in the above application."

Applicants submit that previously the office has not provided any factual evidence to support the Examiner's contention as required in order to refute the Dr. Jack declaration.

Applicants submit that the Examiner has not provided any objective evidence to support his statement concerning "the extreme breadth of the claimed genus".

Applicants continue to question why the Examiner disagrees with applicant's position as stated above and further point to their confusion in light of US 7,541,170.

Applicant's amendment of claim 32 and applicant's complete argument is acknowledged and continues to be carefully considered, however, continues to be found non-persuasive for the reasons previously stated and for those reasons repeated herein.

Applicants continue to argue this rejection on the basis that applicants have limited the claimed methods to those DNA polymerase which share a specified homology to the DNA polymerase encoded by the 5 kb polynucleotide SEQ ID NO: 4 and further comprise a 15 amino acid motif.

As previously stated, the existence of 30% overall identity with that of the polypeptide encoded by SEQ ID NO:4 does not sufficiently reduce the size of the claimed genus such that this requirement in addition to the existence of the referred to 15 amino acid motif does not provide sufficient direction or guidance as to the breadth of the vast number of DNA polymerases encompassed by these structural limitations, Including both known and unknown DNA polymerases.

As previously stated and repeated here, Applicants do not teach that DNA polymerases with 30% overall identity with the polypeptide encoded by of SEQ ID NO:4 and including a 15 amino acid motif identical to one of SEQ ID NOs 5-22 (except for having up to 3 amino acid substitutions) can incorporate acyclonucleotides but rather applicants teach that specific DNA polymerases which have as little as 30% identity to SEQ ID NO: 4 and also include a 15 amino acid motif selected from one of SEQ ID NOs 5-22 can incorporate acyclonucleotides. As previously stated, the identification of the species does not enable the extreme breadth of the claimed genus. Applicants have not refuted this point.

Without sufficient guidance, determination of those DNA polymerases having the desired biological characteristics is unpredictable and the experimentation left to those

skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

It continues that applicants have not enabled the scope of the claimed methods on the basis that applicants have not given guidance as to those DNA polymerases which have the ability to incorporate acyclonucleotides into a DNA template. It is noted that applicant's claims encompass not only methods of use of naturally occurring DNA polymerases, but also variants and mutants thereof a point which applicants have not refuted. As discussed above and previously, applicants have merely identified a few specific DNA polymerases within the 30% sequence identity range that have the necessary acyclonucleotide incorporation function. Such does not enable the breadth of the claimed subgenus of methods of use of the encompassed DNA polymerases which encompasses not only the use of naturally occurring DNA polymerases but also variants and mutants thereof. It remains that applicants have not enabled the extreme breadth of those DNA polymerases so encompassed. Applicants have not enabled the breath of those methods of incorporating acyclonucleotides comprising the use of those DNA polymerases having a mere 30% identity to that polypeptide encoded by SEQ ID NO: 4 and comprising a motif that is selected from the 18 different amino acid sequences listed in SEQ ID NOs: 5-22 and variants thereof. The variability found within the referred to 18 different amino acid sequences does not lend itself to the identification of an amino acid motif.

Again as previously stated, with regard to applicants argument regarding the identification of an amino acid motif domain that is required for this specific function of

acyclonucleotide incorporation, it is noted that applicants specification at page 19, lines 22-24, does not clearly support such. The clarification or expansion of applicant's argument regarding this reference to "the motif" on page 8, line 7 of applicant's argument submitted on 1/9/2009, might be helpful in overcoming this rejection if the referred to "the motif" is shown to correlate with the incorporation of acyclonucleotides. To date this showing has not been clearly established and as such applicants have not enabled the currently claimed methods beyond the taught species. One of the reasons it appears that applicants have not established a correlation between a motif and the acyclonucleotide incorporation function, appears that applicants have not disclosed such a single motif but rather continue to refer to any of a number of motifs or variants thereof.

Beyond the above, without sufficient guidance, determination of those methods and polymerases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 32- 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koster et al . (U.S. patent No. 5,928,906, See IDS submitted on 5/13/2008) and Reid et al. (Journal of Biological Chemistry, Vol 263, pp3896-3904, 1988, See IDS).

This rejection was stated in the previous office action as it applied to previous claims 32-43. In response to this rejection applicants have amended claim 32 and traverse the rejection as it applies to the newly amended claims.

Applicants submit that The examiner's previous statement that:

"The expectation of success is high as everything that is required to perform the made obvious method is taught by the references of Koster et al. and Reid et al... (p. 8 of the office action dated 4/29/10)" is incorrect.

Applicants further state that the reference, Koster et al. is irrelevant since it is well known that vent polymerase has been used in amplification and the claimed method is concerned with the use of acyclonucleotides for chain termination.

Applicants submit that the introduction of the Reid et al. reference as suggesting to a person of ordinary skill in the art that acyclonucleotides would be better than dideoxynucleotides for chain termination in the presence of the claimed polymerases is simply incorrect, on the basis that applicants submit that Reid et al. teach the opposite.

Applicants submit that Evidence has been proffered that the Family B herpes virus type 2 (HSV-2) and human cytomegalovirus (HCMV) DNA polymerases have a preference for insertion of acyclo-GTP over ddGTP (Reid, et al., J. Biol. Chem.

263:3898-3904 (1988)). Applicants further submit that the same report also indicates a strong preference by human DNA polymerase alpha (also a Family B DNA polymerase) for insertion of ddGTP over acyclo-GTP (emphasis added).

Applicants submit that Reid et al. explored various antiviral agents with respect to polymerase-dependent replication including dhpG, acyclovir, dideoxy and arabinosyl nucleoside triphosphates. Reid et al. concluded that there were three contrasting behaviors.

First, extension behavior with araNTP, second insertion/extension behavior with dhpGTP and third the relative preference for insertion of ddGTP versus acyGTP (emphasis added).

Applicants submit that both Applicants and Reid et al. reveal that different classes of polymerases differ in their ability to incorporate different modified nucleotides. Neither Herpes Type 2 nor human cytomeqalovirus studied by Reid et al. are within the scope of the present definition of the polymerases in the claimed invention.

Applicants submit that given the opposite results obtained for the two classes of polymerase examined by Reid et al., there is no basis in the Reid et al. reference to extrapolate the observations to the present claimed class of polymerases which differs from the two classes described by Reid et al.

Applicants submit that the polymerases that fall within the definition are highly conserved Family B archeaon DNA polymerases (page 18 of the specification), which

form a class of enzymes that are understandably distinct from other Type B polymerases such as viral polymerases. Applicants submit that the conserved motif is not a random motif but is described structurally and functionally in the application in great detail on pages 10-15.

Applicant's amendment of the claims and applicants complete argument is acknowledged and has been carefully considered, however, is found non-persuasive for the reasons previously stated and for those reasons repeated herein in response to applicant's response.

Applicant's submission that the examiner's previous statement that:

"The expectation of success is high as everything that is required to perform the made obvious method is taught by the references of Koster et al. and Reid et al... (p. 8 of the office action dated 4/29/10)" is incorrect, is not persuasive on the basis that the expectation of success is high, as everything that is required to perform the claimed method is taught by the references. Applicants are further reminded that this high expectation of success that the examiner previously referred to is relative to that for which the examiner stated was obvious, to practice a method comprising contacting a vent DNA polymerase, as taught by Koster et al., with a template, a primer that binds to said template and a collection of nucleotides and an acyclonucleotide as taught by Reid et al. and incubate the DNA polymerase and template and nucleotides so that the DNA polymerase extends the primer by incorporating the nucleotides, in order to determine the feasibility of using the chain terminating nucleotide, acyclonucleotide, in sequencing

methods with vent DNA polymerase. As stated previously and above, the expectation of success for the above method is high.

Applicants statement that the reference, Koster et al. is irrelevant since it is well known that vent polymerase has been used in amplification and the claimed method is concerned with the use of acyclonucleotides for chain termination is appreciated and acknowledged, however, it is pointed out to applicants that the reference Koster et al. is being used to teach Vent polymerase. Applicant's acknowledgement that this is unnecessary is appreciated.

Applicants submission that the examiner has introduced and characterized the Reid et al. reference as suggesting to a person of ordinary skill in the art that acyclonucleotides would be better than dideoxynucleotides for chain termination in the presence of the claimed polymerases, a statement that applicants submit is simply incorrect, is unclear and confusing. The examiner has reviewed the previous characterization of the Reid et al. reference and such a characterization could not be found and it is noted that such a teaching is an unnecessary part of the current rejection.

Applicant's submission that both Applicants and Reid et al. reveal that different classes of polymerases differ in their ability to incorporate different modified nucleotides is acknowledged.

Applicants submission that given the opposite results obtained for the two classes of polymerase examined by Reid et al., there is no basis in the Reid et al.

reference to extrapolate the observations to the present claimed class of polymerases which differs from the two classes described by Reid et al. is not persuasive as applicants comments are not directed to that which the examiner previously stated was obvious. As previously stated, One of ordinary skill in the art at the time of filing would have been motivated to practice a method comprising 1) providing a vent DNA polymerase, as taught by Koster et al. and 2) contacting the vent DNA polymerase with a template, a primer that binds to said template and a collection of nucleotides and an acyclonucleotide as taught by Reid et al. and 3) incubate the DNA polymerase and template and nucleotides so that the DNA polymerase extends the primer by incorporating the nucleotides, in order to determine the feasibility of using the chain terminating nucleotide, acyclonucleotide, in sequencing methods with vent DNA polymerase.

It is noted that as previously stated by the examiner and repeated above it is obvious to 1) provide the Vent DNA polymerase, 2) contact the polymerase with the acyclonucleotides and 3) incubate the DNA polymerase, acyclonucleotides and additional reaction components. This is the obvious method for which the expectation of success as discussed above is high.

As previously stated, one of ordinary skill in the art at the time of filing would have been motivated to practice a method comprising providing a vent DNA polymerase, as taught by Koster et al. and contacting the vent DNA polymerase with a template, a primer that binds to said template and a collection of nucleotides and an acyclonucleotide as taught by Reid et al. and incubate the DNA polymerase and

template and nucleotides so that the DNA polymerase extends the primer by incorporating the nucleotides, in order to determine the feasibility of using the chain terminating nucleotide, acyclonucleotide, in sequencing methods with vent DNA polymerase. The expectation of success is high as everything that is required to perform the made obvious method is taught by the references of Koster et al. and Reid et al. and the made obvious methods do not require any specific result, but merely the motivation to bring the components of the reaction together and "incubate".

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mondesi Robert can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

rgh
12/21/2010

/Richard G Hutson/
Primary Examiner, Art Unit 1652